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# Vitamin C and Other Compounds in Vitamin C Rich Food in Relation to Risk of Tuberculosis in Male Smokers

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To examine whether vitamin C rich food consumption and related vitamin C intake are associated with the risk of tuberculosis, the authors analyzed 167 incident cases of tuberculosis during a median follow-up time of 6.7 years in a clinical trial cohort of 26,975 Finnish men for whom they had baseline dietary data. A highly statistically significant inverse association between calculated vitamin C intake and the incidence of tuberculosis was found, but adjustment for non-dietary factors weakened the association to nonsignificant. Furthermore, the risk of tuberculosis decreased with increasing intake of fruits, vegetables, and berries independent of vitamin C intake. Subjects who had dietary vitamin C intake >90 mg/day and who consumed more than the average amount of fruits, vegetables, and berries had a significantly lower risk of tuberculosis (adjusted relative risk = 0.40; 95% confidence interval 0.24, 0.69). Associations between dietary vitamin C intake and occurrence of various diseases without proper control of confounding have often been interpreted as causal. These findings show that such associations can be confounded even by some other dietary components. Lower tuberculosis incidence in subjects who consumed more fruits, vegetables, and berries poor in vitamin C suggests that other compounds in such a diet may reduce the risk of tuberculosis. *Am J Epidemiol* 1999;150:632–41.

alpha-tocopherol; ascorbic acid; beta-carotene; body mass index; diet; smoking; tuberculosis

In the first half of the twentieth century, some authors considered that low vitamin C intake may increase the susceptibility to various infections (1–4). In particular, two early studies found that a lower vitamin C intake (5) and a lower vitamin C concentration in plasma (6) were associated with a substantially higher incidence of tuberculosis. In addition, decreased plasma and urine vitamin C levels have been observed in tuberculosis patients (7–10), and laboratory experiments have shown that low vitamin C intake is associated with increased susceptibility to tuberculosis infection in guinea pigs (11–16).

The purpose of the present study was to determine whether dietary vitamin C intake and its source foods are associated with the incidence of tuberculosis in a cohort of Finnish male smokers aged 50–69 years. The cohort was drawn from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, which examined the effects of these substances on the incidence of lung and other cancers (17, 18). Diet and several social and behavioral traits were assessed at study entry and tuberculosis cases that occurred during the follow-up were identified from the national hospital discharge register.

## MATERIALS AND METHODS

### Subjects

The rationale of the design and methods of the ATBC Study to examine the effects of $\alpha$-tocopherol (50 mg/day) and $\beta$-carotene (20 mg/day) on the incidence of lung cancer and other cancers has been described in detail (17, 18). In brief, the trial participants were recruited starting in 1985 from the total male population aged 50–69 years living in southwestern Finland. To be eligible, participants had to smoke at least 5 cigarettes per day at entry. Potential participants were excluded if they had a history of cancer; severe angina on exertion; chronic renal failure; cirrhosis of the liver; chronic alcoholism; anticoagulant therapy; other medical problems that might limit participation for 6 years, such as psychiatric disorder or

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Abbreviations: ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; FRUVEBE, fruit, vegetable, and berry intake; FRUVEBE-RES, residual intake of fruits, vegetables, and berries; ICD, *International Statistical Classification of Diseases, Injuries, and Causes of Death*; RR, relative risk.

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physical disability; and use of supplemental vitamin E, vitamin A, or β-carotene in excess of predefined doses. The eligible participants of the trial ($n$ = 29,133) were randomized to one of four intervention groups and administered placebo, α-tocopherol, β-carotene, or α-tocopherol + β-carotene. The active intervention continued for 5–8 years (median 6.1 years) until April 30, 1993. The trial was approved by the ethical review boards of the participating institutions and all subjects gave written informed consent.

Subjects were excluded who had missing dietary data ($n$ = 2,022), missing body mass index ($n$ = 19), unknown residential neighborhood ($n$ = 6), tuberculosis diagnosed in hospitals before randomization ($n$ = 110), or tuberculosis diagnosed in general practice without confirmation in a hospital ($n$ = 21). This left 26,975 subjects, who made up the study population for the present analysis.

### Baseline characteristics

At baseline prior to randomization, the men completed questionnaires on general background characteristics, medical, and smoking histories, and height and weight were measured. The questionnaires provided data about marital status, residential neighborhood, and education. Body mass index was calculated as weight (kg)/height (m)$^2$.

### Dietary assessment

At the first baseline visit, subjects were given a separate, detailed dietary history questionnaire for completion at home (19), and at the second visit 2 weeks later, the questionnaire was returned and reviewed. The questionnaire included a color picture booklet and asked about portion sizes for 276 common foods and mixed dishes and the usual frequency of their consumption over the previous 12 months. Also, consumption of specific alcoholic beverages was requested and transformed to mean alcohol intake per day. The reproducibility and validity of the dietary assessment method used in the ATBC study was evaluated (19). The daily dietary intake of vitamin C was calculated using the food composition database of the National Public Health Institute (20), which includes correction coefficients for vitamin C destroyed during food preparation. Median dietary vitamin C intake was 90 mg/day. The total daily consumption of fruits, vegetables, and berries was calculated for this study. Median fruit, vegetable, and berry intake was 183 g/day.

The use of vitamin C supplements was inquired at the baseline visit and at the 4-month follow-up visits. Only 1,253 subjects (4.6 percent) reported that they used any vitamin C supplements at both the baseline and the first follow-up visits, the median doses being 90 and 75 mg/day, respectively, for these subjects. Furthermore, only 341 subjects (1.3 percent) reported that they used vitamin C supplements with doses over 50 mg/day at each follow-up visit for 2 years. Of these 341 subjects, 35 percent fell into the highest quartile of dietary intake and 18 percent fell into the lowest quartile. Accordingly vitamin C supplement usage was rare in our study group, the doses used were small, and the consumption was more common among subjects who obtained higher intakes in their diet. Thus, ignoring supplement usage in our analyses did not cause considerable misclassification in the vitamin C intake groups. Supplemental vitamin C intake was also ignored when calculating the dietary vitamin C intakes.

### Study endpoint

The endpoint for this study, clinical diagnoses of tuberculosis after dietary assessment, was searched from the Hospital Discharge Register using the unique personal identity number for linkage. The National Agency for Welfare and Health has kept a national register of hospital discharges since 1967 (21). The register covers all discharges of inpatients from all hospitals, both public and private, in Finland, and uses the codes of the *International Statistical Classification of Diseases, Injuries, and Causes of Death* (ICD). The 8th edition (ICD-8) was used to the end of 1986 and the 9th edition (ICD-9) thereafter. Up to four diagnoses per each discharge are recorded in the register. The validity of the Finnish Hospital Discharge Register was recently examined from a random sample of 2,211 discharges (21). The registered cause of hospitalization was compared with the medical records and in 94 percent of cases the same diagnosis was reached. In the category of infections, the agreement was 88 percent. Among infections, tuberculosis is particularly well defined and therefore the accuracy evidently is considerably higher than in other infections.

There were 167 cases of new tuberculosis (ICD codes 010–018) from 1985 to the end of 1993. In 140 cases, tuberculosis was the primary diagnosis for the hospital stay, and in 27 cases it was a secondary diagnosis. In 154 cases, tuberculosis was in the respiratory tract (ICD-8 and ICD-9 codes 010–012). These included two cases of primary tuberculosis (010), 130 cases of pulmonary tuberculosis (011), and 22 cases of tuberculosis elsewhere in the respiratory tract (012). In 13 cases, tuberculosis was in other organs (013–018). The tuberculosis diagnoses of ICD-9 codes 010–016 and 018 also include explicit information about whether tuberculosis was bacteriologically or histologically confirmed, and there were 74 such cases among 151 cases with the ICD-9 codes. For cases with ICD-8 codes ($n$ = 16), there were no bacteriologic or histologic data available.

### Statistical methods

Each participant's follow-up time began from the day dietary assessment was completed, and continued until the date of hospital discharge for tuberculosis, death, or end of follow-up in December 1993, whichever came first. The registration of hospital stays occurred independent of whether or not a subject continued in the trial. The median follow-up time of the subjects in the present analysis was 6.7 years and there were a total of 173,015 person-years of observation.

The adjusted relative risks were estimated with the proportional hazards regression model (22). The 95 percent confidence interval of the relative risk estimate was derived from the following formula:

$$95\%\ \mathrm{CI}_{\mathrm{low,high}} = \exp(\beta \pm 1.96 \times \mathrm{SE}(\beta)), \qquad (1)$$

where $\beta$ is the regression coefficient and SE($\beta$) is its standard error. The calculations were carried out with the use of PC-SAS software (release 6.12, SAS Institute, Inc., Cary, North Carolina).

Categorizations of the potential confounding factors are given in table 1. Body mass index and the number of cigarettes smoked per day were used as continuous variables in the models analyzing the role of diet.

The major vitamin C sources in the diet of the study subjects were fruits, vegetables, and berries, on average 58 percent of calculated dietary vitamin C originating from these foods. The total intake of fruits, vegetables, and berries (FRUVEBE) was strongly correlated with the calculated vitamin C intake ($r$ = 0.88). To analyze the possible effects of dietary substances other than vitamin C in these foods, the variation in FRUVEBE was divided into two component variables: dietary vitamin C intake and the residual FRUVEBE intake (FBUVEBE-RES). FRUVEBE was modeled as a function of vitamin C by linear regression analysis, and the FRUVEBE-RES was calculated from the difference between the linear model and the FRUVEBE as follows:

$$\mathrm{FBUVEBE\text{-}RES}\ [\mathrm{g/day}] = \mathrm{FRUVEBE}\ [\mathrm{g/day}] -$$

$$2.47 \times \mathrm{vitamin\ C}\ [\mathrm{mg/day}] + 35.4\ [\mathrm{g/day}]. \qquad (2)$$

FRUVEBE-RES had no correlation with dietary vitamin C. The FRUVEBE-RES quartiles were –34.0, –2.6, and 31.8 g/day, which were used in the division of subjects into four FRUVEBE-RES groups. FRUVEBE-RES below median indicates that the subject consumes fruits, vegetables, and berries rich in vitamin C. FRUVEBE-RES above median indicates that the respective food classes are poor in vitamin C. It is assumed that any other putative compound affecting the susceptibility to tuberculosis has no perfect linear correlation with vitamin C and therefore the variation in such other substances remains as variation in FRUVEBE-RES.

The statistical significance of the trend of tuberculosis incidence with change in vitamin C, FRUVEBE, and FRUVEBE-RES variables (tables 2 and 3) was calculated as follows. To decrease the weight of distant points, square roots of the dietary variables were calculated (the sign of the FRUVEBE-RES was restored after taking the square root of the absolute value) and the transformed value was included in the statistical model as a continuous variable. The associated $p$ value (two-tailed) was obtained from the Wald test.

## RESULTS

During 173,015 person-years of follow-up of the study subjects, there were 167 cases of hospital-diagnosed tuberculosis. The characteristics of the subjects are shown in table 1. Smoking, age, body mass index, residential neighborhood, and marital status were important predictive factors for tuberculosis and were considered as potential confounders (table 1). Alcohol intake was found not to be associated and education only weakly associated with risk of tuberculosis. The risk of tuberculosis in the $\alpha$-tocopherol and $\beta$-carotene supplementation groups did not significantly differ from that in the placebo group. The expected number of tuberculosis cases (assuming average incidence) among the 341 subjects who regularly consumed vitamin C supplements at a dose >50 mg/day was 2.2, whereas three cases were observed.

Subjects were divided into four groups by the quartiles of dietary vitamin C intake (table 2). A significantly lower unadjusted risk of tuberculosis (relative risk (RR) = 0.52; 95 percent confidence interval (CI) 0.33, 0.82) was observed among subjects in the highest quartile of vitamin C intake compared with the lowest quartile. There was a statistically significant trend toward a lower unadjusted risk with increasing dietary vitamin C intake ($p$ = 0.005). After adjustment for age and smoking, the difference between the highest and lowest quartile was slightly reduced but remained significant (RR = 0.58; 95 percent CI 0.37, 0.92). However, this difference became smaller and nonsignificant when body mass index, residential neighborhood, and marital status were further added to the statistical model (RR = 0.70; 95 percent CI 0.44, 1.10; table 2).

**TABLE 1. Association of baseline characteristics with the incidence of tuberculosis in Finnish men: the ATBC Study,* 1985–1993**

| Characteristic | Total subjects (%) (*n* = 26,975) | Cases of tuberculosis (%) (*n* = 167) | Adjusted RR*,† | 95% CI* |
|---|---|---|---|---|
| Age (years) | | | | |
| 50–59 | 68 | 54 | 1.00‡ | |
| 60–69 | 32 | 46 | 1.83 | 1.34, 2.51 |
| Body mass index (kg/m²) | | | | |
| <23 | 19 | 38 | 1.00‡ | |
| 23–27 | 42 | 40 | 0.48 | 0.34, 0.68 |
| >27 | 39 | 22 | 0.29 | 0.19, 0.44 |
| Marital status | | | | |
| Married | 81 | 72 | 1.00‡ | |
| Never married | 5 | 6 | 1.08 | 0.56, 2.07 |
| Divorced | 10 | 14 | 1.68 | 1.07, 2.63 |
| Widowed | 4 | 8 | 2.12 | 1.19, 3.79 |
| Education | | | | |
| ≤Elementary school | 78 | 84 | 1.00‡ | |
| >Elementary school | 22 | 16 | 0.74 | 0.48, 1.12 |
| Residential neighborhood | | | | |
| City or town | 64 | 53 | 1.00‡ | |
| Village or countryside | 36 | 47 | 1.69 | 1.24, 2.31 |
| Cigarettes (1/day) | | | | |
| ≤15 | 33 | 26 | 1.00‡ | |
| 16–25 | 49 | 50 | 1.37 | 0.94, 1.98 |
| ≥26 | 18 | 24 | 2.11 | 1.36, 3.29 |
| Alcohol (g/day) | | | | |
| <30 | 80 | 80 | 1.00‡ | |
| ≥30 | 20 | 20 | 1.03 | 0.70, 1.53 |
| Supplementation group | | | | |
| Placebo | 25 | 22 | 1.00‡ | |
| β-Carotene | 25 | 25 | 1.09 | 0.70, 1.70 |
| α-Tocopherol | 25 | 27 | 1.23 | 0.80, 1.90 |
| α-Tocopherol + β-Carotene | 25 | 26 | 1.15 | 0.74, 1.79 |

* ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.

† For each variable, RR was adjusted for the effects of all other variables in the table.

‡ Reference category.

Fruits, vegetables, and berries were the main sources of vitamin C for the study subjects. The total intake of fruits, vegetables, and berries had a strong negative association with the risk of tuberculosis (table 2). The unadjusted risk was significantly lower in the highest quartile when compared with the lowest quartile of intake (RR = 0.39; 95 percent CI 0.24, 0.63). Because it is possible that dietary constituents other than vitamin C could affect the risk of tuberculosis, we calculated the residual fruit, vegetable, and berry intake. A negative residual indicates that the vitamin C intake arises from a smaller than average total amount of fruits, vegetables, and berries consumed, i.e., the subject consumes a variety of fruits, vegetables, and berries that are rich in vitamin C. In contrast, a positive residual intake indicates that the subject consumes fruits, vegetables, and berries that are poor in vitamin C. Subjects in the highest residual fruit, vegetable, and berry intake quartile had a significantly lower unadjusted risk of tuberculosis (RR = 0.44; 95 percent CI 0.28, 0.70) when compared with the lowest quartile of intake (table 2). After adjustment for all confounding factors, the association between residual fruit, vegetable, and berry intake and tuberculosis incidence was statistically substantially stronger ($p$ = 0.004) than the association between vitamin C and tuberculosis incidence ($p$ = 0.18). This suggests there may be other compounds than vitamin C in fruits, vegetables, and berries that influence the risk of developing tuberculosis.

The association between dietary vitamin C intake and the risk of tuberculosis was further analyzed by dividing each vitamin C group separately into four groups by the quartiles of residual fruit, vegetable, and berry intake (table 3). If vitamin C intake per se has an effect on tuberculosis risk, a negative association between vitamin C intake and tuberculosis incidence would be expected among subjects who consumed fruits, vegetables, and berries rich in vitamin C. In the

**TABLE 2. Risk of tuberculosis by vitamin C intake and by fruit, vegetable, and berry consumption in Finnish men: the ATBC Study,* 1985–1993**

| | Intake by quartile | | | | *p* value for trend |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Vitamin C | | | | | |
| Mean (mg/day) | 50 | 78 | 104 | 161 | |
| Tuberculosis cases (no.) | 54 | 44 | 40 | 29 | |
| Crude RR* | 1.00‡ | 0.80 | 0.72 | 0.52 | 0.005 |
| 95% CI* | | 0.54, 1.19 | 0.48, 1.09 | 0.33, 0.82 | |
| Adjusted RR† | 1.00‡ | 0.91 | 0.89 | 0.70 | 0.18 |
| 95% CI | | 0.61, 1.36 | 0.59, 1.35 | 0.44, 1.10 | |
| Fruits, vegetables, and berries | | | | | |
| Mean (g/day) | 73 | 149 | 224 | 384 | |
| Tuberculosis cases (no.) | 57 | 49 | 38 | 23 | |
| Crude RR | 1.00‡ | 0.84 | 0.65 | 0.39 | 0.00005 |
| 95% CI | | 0.57, 1.23 | 0.43, 0.98 | 0.24, 0.63 | |
| Adjusted RR† | 1.00‡ | 0.97 | 0.81 | 0.53 | 0.015 |
| 95% CI | | 0.66, 1.42 | 0.53, 1.22 | 0.33, 0.87 | |
| Residual of fruits, vegetables, and berries§ | | | | | |
| Mean (g/day) | –70 | –18 | 13 | 76 | |
| Tuberculosis cases (no.) | 57 | 44 | 40 | 26 | |
| Crude RR | 1.00‡ | 0.76 | 0.69 | 0.44 | 0.0006 |
| 95% CI | | 0.51, 1.13 | 0.46, 1.03 | 0.28, 0.70 | |
| Adjusted RR† | 1.00‡ | 0.75 | 0.70 | 0.50 | 0.004 |
| 95% CI | | 0.50, 1.11 | 0.47, 1.05 | 0.31, 0.79 | |

* ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.

† Adjusted for effects of smoking, age, marital status, residential neighborhood, and body mass index by proportional hazards model.

‡ Reference group.

§ Negative residual corresponds to "vitamin C rich" foods and positive residual to "vitamin C poor" foods at a given vitamin C intake.

two lowest residual intake quartiles (1 and 2), there was no association between tuberculosis incidence and vitamin C intake, which suggests that vitamin C per se has no effect on the susceptibility to tuberculosis (table 3). Independently of vitamin C, the intake of fruits, vegetables, and berries appears to affect tuberculosis risk, because we observed a statistically significant decrease in the tuberculosis risk with increase in the residual intake of fruits, vegetables, and berries in the two highest vitamin C intake quartiles (table 3).

In table 3, the columns are limited by fixed vitamin C intake levels. However, the residuals in the rows of data are not constant but increase in absolute terms with an increase in vitamin C intake levels. In addition, total intake of fruits, vegetables, and berries in the rows increases with vitamin C intake. To show the actual fruit, vegetable, and berry intake in the 16 groups of table 3, we plotted the groups on a plane according to total fruit, vegetable, and berry intake and vitamin C intake (figure 1). Starting from the reference group (RR = 1.00), and keeping the amount of fruits, vegetables, and berries fixed at around 280 g/day, a decrease in vitamin C intake leads to a decrease in the risk of tuberculosis (to RR = 0.29, 0.51, and 0.60). A similar trend is seen at an intake of around 140 g/day. Thus, an increase in vitamin C intake does not decrease the risk of tuberculosis when the intake of total fruits, vegetables, and berries is kept fixed. The three groups that had the lowest risk of tuberculosis (RR = 0.29, 0.31, and 0.32), in addition to having a high residual intake, also had a high total intake of fruits, vegetables, and berries (averages of 236, 370, and 484 g/day, respectively). In comparison, in the lowest vitamin C quartile, persons in the highest fruit residual quartile (RR = 0.61) consume an average of only 134 g/day of fruits.

We observed a significant association between intake of fruits, vegetables, and berries and tuberculosis risk among subjects in the two highest quartiles of vitamin C. As a result of this finding, these subjects were analyzed in more detail (table 4). Subjects were divided into two groups, i.e., subjects who consumed vitamin C poor fruits, vegetables, and berries (residual above median) and those who consumed vitamin C rich foods (residual below median), which resulted in identical mean dietary vitamin C intake in both groups.

**TABLE 3. Association of vitamin C intake, and the residual fruit, vegetable, and berry consumption with tuberculosis incidence in Finnish men: the ATBC Study,* 1985–1993**

| Intake of residual fruits, vegetables, and berries by quartile† | Vitamin C intake by quartile† (range, mg/day) 1 (5–66) | 2 (66–90) | 3 (90–121) | 4 (121–534) | *p* value for trend |
|---|---|---|---|---|---|
| 4. (High) | | | | | |
| Tuberculosis cases (no.) | 10 | 9 | 7 | 4 | |
| Adjusted RR*,‡ | 0.61 | 0.60 | 0.51 | 0.32 | 0.20 |
| 95% CI* | 0.27, 1.38 | 0.26, 1.40 | 0.21, 1.28 | 0.10, 0.97 | |
| 3. | | | | | |
| Tuberculosis cases (no.) | 18 | 11 | 4 | 4 | |
| Adjusted RR‡ | 1.04 | 0.73 | 0.29 | 0.31 | 0.007 |
| 95% CI | 0.52, 2.11 | 0.33, 1.61 | 0.09, 0.87 | 0.10, 0.94 | |
| 2. | | | | | |
| Tuberculosis cases (no.) | 12 | 11 | 11 | 7 | |
| Adjusted RR‡ | 0.69 | 0.73 | 0.74 | 0.52 | 0.63 |
| 95% CI | 0.32, 1.50 | 0.33, 1.60 | 0.34, 1.64 | 0.21, 1.29 | |
| 1. (Low) | | | | | |
| Tuberculosis cases (no.) | 14 | 13 | 18 | 14 | |
| Adjusted RR‡ | 0.81 | 0.82 | 1.22 | 1.00§ | 0.34 |
| 95% CI | 0.39, 1.71 | 0.38, 1.74 | 0.60, 2.45 | | |
| *p* value for trend | 0.82 | 0.63 | 0.009 | 0.032 | |

* ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.

† Within each vitamin C intake quartile, the subjects were divided into four groups by the quartiles of residual fruit, vegetable, and berry intake to create 16 groups of similar size. The number of subjects in the groups varies between 1,685 and 1,687.

‡ Adjusted for effects of smoking, age, marital status, residential neighborhood, and body mass index by proportional hazards model.

§ Reference group.

A significantly lower risk of tuberculosis was observed among subjects who consumed vitamin C poor foods (RR = 0.36) compared with subjects who consumed vitamin C rich foods. The inclusion of potential nondietary confounding factors in the model had no substantial effect on the relative risk estimate (adjusted RR = 0.40). In this restricted set of subjects, a reduced risk of tuberculosis was also observed when the analysis was limited to subjects with pulmonary tuberculosis as a primary hospital diagnosis ($n$ = 46) (adjusted RR = 0.33; 95 percent CI 0.16, 0.65) and to subjects in which tuberculosis was confirmed bacteriologically or histologically ($n$ = 33) (adjusted RR = 0.48; 95 percent CI 0.22, 1.01).

The possibility of effect modification was examined by dividing the subjects in the two highest quartiles of vitamin C into subgroups on the basis of smoking, age, and body mass index. Among subjects who consumed vitamin C rich foods and who smoked at least 20 cigarettes per day, we found an increased risk of tuberculosis (adjusted RR = 2.53) when compared with subjects who consumed vitamin C rich foods and who smoked less (table 5). Heavy smokers who consumed vitamin C rich foods had a tuberculosis incidence rate (148 cases/$10^5$ person-years) substantially higher than the rates in the three other groups (34–69 cases/$10^5$ person-years). In the regression model that adjusted for counfounders, the interaction term between smoking and residual intake was statistically significant ($p$ = 0.03). Thus, the combination of heavy smoking and compounds other than vitamin C in fruits, vegetables, and berries explain much of the differences in tuberculosis risk in these subjects. Age and body mass index did not significantly modify the effect when age 60 years and body mass index 26 kg/m$^2$ were used as cutoff limits (data not shown).

## DISCUSSION

*Mycobacterium tuberculosis* is an intracellular pathogen, and protection against the pathogen is accomplished by cell-mediated immunity (23). In a few human studies, vitamin C administration increased the proliferative responses of T-lymphocytes (4, 24–28), but not in other studies (29, 30). Vitamin C may also affect phagocytosis and chemotaxis of macrophages and neutrophils (4, 31–37). The disease preventive significance of these immunologic effects

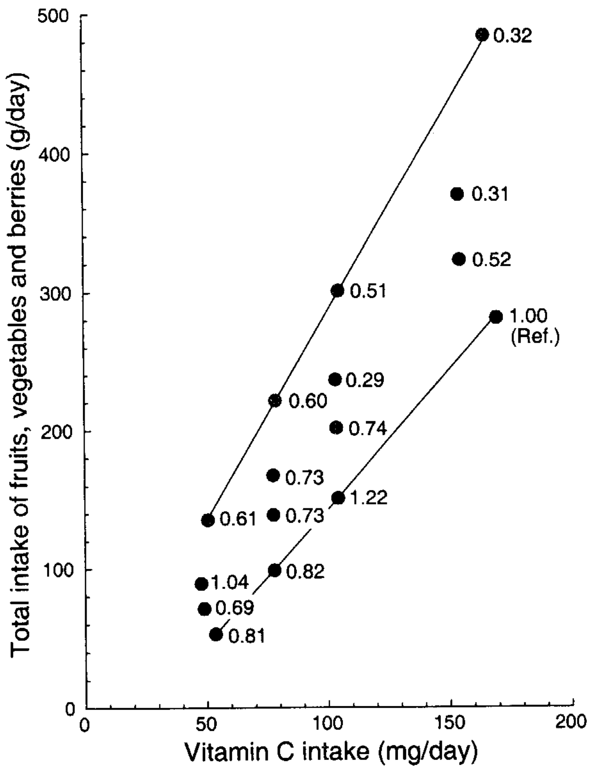


**FIGURE 1.** Risk of tuberculosis in groups of Finnish men according to their vitamin C intake, and the total intake of fruits, vegetables, and berries: the ATBC Study, 1985–1993. The 16 groups shown in table 3, based on vitamin C intake and residual intake of fruits, vegetables, and berries, are here indicated by circles located at the mean value of vitamin C intake, and the mean value of total fruit, vegetable, and berry intake. The corresponding adjusted relative risk estimates are shown to the right of the circles. The highest and lowest quartiles of residual fruit, vegetable, and berry intake are connected with lines. On this plane, the groups of table 3 are not rectangles, but rhomboids with straight vertical edges, and upper and lower edges closely parallel with the marked lines.

is not clear. Nevertheless, in several controlled studies, vitamin C supplementation decreased incidence of the common cold (38, 39) and pneumonia (40) and reduced the severity of common cold episodes (41–44), which suggests that the vitamin may have relevant effects on the immune system, although the mechanisms and the practical importance of these findings are poorly understood.

Low level of vitamin C intake decreased the resistance of guinea pigs to *M. tuberculosis* (11–16). Two older studies in young and middle aged blacks in the United States reported a lower incidence of tuberculosis in subjects with higher vitamin C intake. In an intervention study by Downes (5), there was only one case of tuberculosis during 644 person-years of follow-up of subjects who were administered vitamin C (20–400 mg/day), but 10 cases during 1,096 person-years in the control group. However, certain other nutrients were also administered and therefore the difference between

**TABLE 4. Risk of tuberculosis in Finnish men with vitamin C intake >90 mg/day: the ATBC Study,* 1985–1993**

| | Fruits, vegetables, and berries† | |
|---|---|---|
| | Rich in vitamin C ($n$ = 6,620) | Poor in vitamin C ($n$ = 6,868) |
| Vitamin C, mean (mg/day) | 133 | 132 |
| Fruits, vegetables, and berries, mean (g/day) | 238 | 346 |
| Tuberculosis cases (no.) | 50 | 19 |
| Rate (cases/$10^5$ person-years) | 118 | 42 |
| Crude RR* | 1.00§ | 0.36 |
| 95% CI* | | 0.21, 0.61 |
| Adjusted RR‡ | 1.00§ | 0.40 |
| 95% CI | | 0.24, 0.69 |

* ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.
† Fruits, vegetables, and berries poor in vitamin C refers to residual intake of fruits, vegetables, and berries (FRUVEBE-RES) above median, and rich in vitamin C refers to FRUVEBE-RES below median (cf. equation 2).
‡ Adjusted for effects of smoking, age, marital status, residential neighborhood, and body mass index by proportional hazards model.
§ Reference group.

the two groups cannot be attributed to vitamin C alone. In a prospective cohort study, Getz et al. (6) found no cases of tuberculosis among 177 subjects with an initial plasma vitamin C level higher than 6 mg/liter, but 27 cases among 896 subjects with a lower vitamin C level. Such an association could, however, be caused by other dietary or non-dietary factors associated with vitamin C.

In the present study, the association between dietary vitamin C intake and the incidence of hospital-diagnosed tuberculosis cases was studied in the cohort of the ATBC Study composed of 50–69-year-old Finnish male smokers. The overall average annual case rate in this study population was 96 per 100,000. Although this may seem unrealistically high to anyone who knows how low the overall case rate is at the present time in Finland, it should be remembered that in the early years of this century, Finland had one of the highest tuberculosis rates in Europe. The men in the study group were 50–70 years of age in the 1980s and had lived their early years at a time when tuberculosis was much more common in Finland than it is now. Cohort studies in Finland have shown that a case rate of 96 per 100,000 is approximately what would be expected for men of this age, and that the rates of reinfections for their birth cohort have been decreasing but still reflect high rates in the past (45).

In an unadjusted analysis, there was a statistically highly significant trend toward a lower incidence of

**TABLE 5. Risk of tuberculosis in Finnish men with vitamin C intake >90 mg/day according to cigarette smoking: the ATBC Study,* 1985–1993**

| Cigarette smoking | Fruits, vegetables, and berries† Rich in vitamin C ($n$ = 6,620) | Poor in vitamin C ($n$ = 6,868) |
|---|---|---|
| ≤19 cigarettes/day | | |
| Tuberculosis cases (no.) | 11 | 10 |
| Rate (cases/10⁵ person-years) | 69 | 54 |
| Adjusted RR*,‡ | 1.00§ | 0.91 |
| 95% CI* | | 0.38, 2.15 |
| ≥20 cigarettes/day | | |
| Tuberculosis cases (no.) | 39 | 9 |
| Rate (cases/10⁵ person-years) | 148 | 34 |
| Adjusted RR‡ | 2.53 | 0.63 |
| 95% CI | 1.29, 4.97 | 0.26, 1.55 |

* ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; RR, relative risk; CI, confidence interval.

† Fruits, vegetables, and berries poor in vitamin C refers to residual intake of fruits, vegetables, and berries (FRUVEBE-RES) above median, and rich in vitamin C refers to FRUVEBE-RES below median (cf. equation 2).

‡ Adjusted for effects of age, marital status, residential neighborhood, and body mass index by proportional hazards model. Subjects who consumed vitamin C rich foods and smoked <20 cigarettes per day were used as a reference group. When the dichotomous interaction term of heavy smoking (≥20 cigarettes/day) and vitamin C rich fruit, vegetable, and berry intake (residual below median) was added to the model, the −2 x log (likelihood) increased by 5.15 ($p$ = 0.03).

§ Reference group.

tuberculosis among subjects with higher vitamin C intake, which became nonsignificant after adjustment for confounders. Dietary vitamin C of the subjects was derived primarily from fruits, vegetables, and berries. Other compounds in such foods could be responsible for the modest inverse association between vitamin C intake and tuberculosis incidence. We calculated residual fruit, vegetable, and berry intake in order to generate a variable that reflects the variation of constituents other than vitamin C in these foods. Residual intake of fruits, vegetables, and berries did not correlate with dietary vitamin C intake, yet the residual also showed an association with tuberculosis incidence substantially stronger than vitamin C intake after controlling for confounding (table 2). This result suggests that in fruits, vegetables, and berries there are compounds other than vitamin C that affect susceptibility to tuberculosis. Furthermore, a higher intake of vitamin C rich foods, corresponding to a negative residual, was not associated with reduced tuberculosis risk (table 3 and figure 1), indicating even more directly that vitamin C intake per se had no effect on tuberculosis incidence in the study subjects. Although figure 1 appears to indicate an increase in tuberculosis risk with increase in vitamin C intake at around 140 and 280 g/day of fruits, vegetables, and berries, this apparent trend with the increased vitamin C intake may result partly from differences in the kinds of fruits, vegetables, and berries which contain different compounds other than vitamin C, and partly from unadjusted confounding factors. Therefore, we do not consider that the observed trend should be considered an indication that vitamin C actually increases tuberculosis risk.

Increased intake of vitamin C poor fruits, vegetables, and berries were associated with a reduced risk of tuberculosis, presumably due to substances in these foods other than vitamin C (table 3). This interpretation was further supported when we limited analysis to subjects with vitamin C intake >90 mg. Intake of vitamin C poor fruits, vegetables, and berries was associated with a considerably lower risk of tuberculosis (table 4). In this case, mean vitamin C intake was similar in both comparison groups. Subgroup analysis suggested that the kind of fruit, vegetable, and berry intake had a greater effect among subjects who smoked at least a pack of cigarettes per day compared with subjects who smoked less (table 5).

Our findings do not support the hypothesis that vitamin C intake affects the susceptibility to tuberculosis. Nevertheless, we conclude that other compounds in diet may have a substantial effect on the susceptibility to tuberculosis in subjects comparable with those of this study. In table 4, the division criterion between the two groups is explicitly based on the differences in the kind of diet between the two groups. Although there evidently are other than dietary differences between the two groups, the inclusion of known non-dietary confounders caused only a minor effect on the estimated relative risk (from 0.36 to 0.40). It seems unlikely that there are unidentified non-dietary differences between the two groups that could create spurious association of this magnitude. Measurement of food intake is never highly accurate, and accordingly there could have been classification errors among the groups of subjects used in the analyses. Additionally, it is possible that there may have been some false positive or negative diagnoses of tuberculosis. However, such classification errors would tend to move the relative risk toward unity rather than away from it. It is unlikely that misclassification explains the observed association in table 4; the true effect may be even greater than that suggested by the relative risk estimates. Although the difference in tuberculosis risk in table 4 appears to be explained by the dietary differences between the two groups, it is not clear which specific constituents of fruits, vegetables, and berries are responsible for the difference in tuberculosis risk between the two groups. The lack of effect by α-tocopherol and β-carotene supplementation in the controlled trial suggests that these two substances do not have important physiologic effects on susceptibility to tuberculosis.

Numerous observational studies have found that low vitamin C intake or plasma level is associated with increased risk of cancers, cardiovascular diseases, stroke, elevated blood pressure, and pulmonary function (46–60). In many studies, only a few potential confounding factors were taken into account, such as sex, age, and smoking. In our study restricted to men, the association between dietary vitamin C intake and tuberculosis incidence was statistically significant after adjusting for age and smoking. However, when we further adjusted for body mass index, residential neighborhood, and marital status, no meaningful association remained between vitamin C intake and tuberculosis incidence (table 2). Moreover, the weak negative association between vitamin C intake and tuberculosis risk that remained after adjustment was explained by other constituents of foods that contained vitamin C (tables 3 and 4). Thus, controlling for numerous non-dietary confounding factors cannot guarantee that vitamin C intake per se is associated with the risk of disease because any diet rich in vitamin C contains high amounts of many other dietary compounds that could have potential effects. Accordingly, great care should be exercised not to overinterpret an association between calculated vitamin C intake and risk of a disease. Too often dietary advice is given to the public based on insufficient evidence from poorly controlled studies.

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